Clinical Results with Direct Thrombin Inhibitors

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Key Words

Direct thrombin inhibitors · Hirudin

Abstract

Direct thrombin inhibitors inactivate thrombin without the need for antithrombin and some inactivate not only thrombin but also fibrin-bound thrombin. Hirudin has been shown to be more effective than low-dose unfractionated heparin and low molecular weight heparin for the prevention of deep vein thrombosis in high-risk orthopaedic patients. Major studies are assessing the value of direct thrombin inhibitors in patients with acute coronary syndromes. Currently, argatroban is the drug of choice in patients with heparin-induced thrombocytopenia.

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Introduction

The established anticoagulant agents, unfractionated heparin, oral anticoagulants and aspirin are effective, but have limitations. Unfractionated heparin has a narrow therapeutic window and a variable dose response because it binds with plasma proteins and proteins released from platelets. The effect of oral anticoagulants such as warfarin is also erratic. Thus, both require monitoring. In addition, unfractionated heparin is unable to inactivate thrombin bound to fibrin [1] and factor Xa bound to acti-

vated platelets trapped within the thrombus [2]. These enzymes may cause thrombus growth once treatment is stopped. Another disadvantage is the development of heparin-induced thrombocytopenia.

The above limitations have stimulated the search for newer antithrombotic drugs and advances in biotechnology and molecular biology have made possible the development of low molecular weight (LMW) heparin and direct thrombin inhibitors, which have a predictable dose response. Also, the limitations of aspirin whose effect is based on the inhibition of thromboxane A₂ synthesis have been overcome by the development of new platelet inhibitors which inhibit ADP-induced platelet activation (ticlopidine, clopidogrel) or glycoprotein IIb/IIIa antagonists which block platelet aggregation in response to all agonists.

The aim of this review is to summarize the development and clinical potential of direct thrombin inhibitors.

Properties of Direct Thrombin Inhibitors

Direct thrombin inhibitors inactivate thrombin without the need for antithrombin to be present. In addition they inactivate thrombin bound to fibrin and thrombomodulin [1, 3]. In contrast to unfractionated heparin, they are not neutralized by platelet factor 4 (PF4), they do not bind to plasma proteins and as a consequence. They have a predictable anticoagulant response. Another advantage is that they do not cause immunologically mediated thrombocytopenia.

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Direct Thrombin Inhibitors in Clinical Use

Hirudin is the oldest known direct thrombin inhibitor. It is a 65-amino-acid polypeptide initially isolated from the saliva of medicinal leeches, but is now produced by recombinant DNA technology (lepirudin/desirudin). Bivalirudin (previously known as hirulog) is an LMW synthetic 20-amino-acid polypeptide. Both bind to thrombin at exosite 1 (the substrate recognition site) and to the active site. By inactivating not only thrombin but also fibrin-bound thrombin they inhibit thrombin-induced platelet activation. Other LMW preparations binding only to the active site are argatroban, efegatran, inogatran and melagatran.

H376/95 is the prodrug form of melagatran, which can be given orally. It is a small molecule (MW = 474) rapidly absorbed, producing peak levels in 15–30 min with melagatran peak levels of 1–2 h. It has a bioavailability of 20% and a predictable dose response.

Efficacy in the Prevention of Deep Vein Thrombosis

In a randomized controlled phase 3 clinical trial, hirudin was found to be more effective than LMW heparin for the prevention of DVT in high-risk orthopedic patients [4]. The oral form (H376/95) of melagatran has been shown to be more effective in the prevention of venous thromboembolism (odds ratio 0.45) than dalteparin in patients having hip and knee replacement (The METHRO II study).

Effect on Restenosis following Coronary Angioplasty

In a study by Serruys et al. [5], 1,141 patients undergoing coronary angioplasty were randomized to hirudin or unfractionated heparin. Hirudin reduced the early (96-hour) cardiac events from 11% in the unfractionated heparin group to 5.5% in the hirudin group ($p = 0.023$). However, there was no difference in the event-free survival at 7 months.

Effect in Patients with Acute Coronary Syndromes

A number of moderate-sized studies using direct thrombin inhibitors in patients who were and were not receiving thrombolytic therapy were performed in the

1990s. They suggested that direct thrombin inhibitors were safe, had dose-dependent anticoagulation efficacy and improved angiographic findings [7–15].

On the basis of these findings three large subsequent studies tested hirudin against unfractionated heparin (GUSTO IIb, 1996; OASIS-1, 1997; OASIS-2, 1999) [16–18] in patients with non-ST-segment elevation acute coronary syndromes. There were 503 patients in GUSTO II b, 909 in OASIS-1 and 10,141 in OASIS-2. Pooled analysis of these three studies demonstrated that the risk of death at 7 days was reduced by 28% in the hirudin group but there was no difference at 35 days. In the OASIS-2 study major bleeding was common with hirudin, although the numbers of life-threatening episodes and hemorrhagic strokes were similar.

The value of direct thrombin inhibitors as adjunctive therapy in patients with ST segment elevation treated with thrombolytic therapy was investigated in several large trials. Three trials using relatively high doses of hirudin (HIT, GUSTO IIa, TIMI 9a) [19–21] were stopped prematurely because of an unacceptably high incidence of intracranial hemorrhage. The TIMI 9a and the GUSTO IIa trials were redesigned as the TIMI 9b and GUSTO IIb comparing lower doses of hirudin with unfractionated heparin.

In the TIMI 9b, 3,002 patients were randomized to 5,000 IU heparin as a bolus followed by 1,000 IU/h intravenously or hirudin (desirudin) 0.1 mg/kg bolus followed by 0.1 mg/kg/h. Both regimens were given for 96 h. The composite rate of death, myocardial infarction and refractory angina was 11.9% in the unfractionated heparin group and 12.9% in the hirudin group. In the GUSTO IIb trial, death or myocardial infarction at 30 days was 11.3% in the heparin group and 9.9% in the hirudin group. The conclusion was that in both studies both regimens were equally effective [22].

Preliminary studies of other direct thrombin inhibitors as adjuvant therapy in patients receiving thrombolytic therapy have produced conflicting results [23–26]. The HERO-Acute MI study randomized 412 patients into 5,000 IU of unfractionated heparin as a bolus followed by 1,000 IU/h or hirulog (low dose) 0.125 mg/kg bolus followed by 0.25 mg/kg/h for the first 12 h and subsequently 0.125 mg/kg/h up to 60 h or hirulog (high dose) 0.25 mg/kg bolus followed by 0.5 mg/kg/h for 12 h and subsequently 0.25 mg/kg/h up to 60 h. The results indicated that the high dose of hirulog in combination with streptokinase achieved TIMI grade 3 coronary flow in a higher percentage of patients at 90–120 min (48 vs. 35%). At 35 days, a 20–30% reduction was observed in the incidence of

death, MI and cardiogenic shock in the hirulog group, but it was not statistically significant. In view of this trend, the HERO-2 trial has been set up which is currently assessing clinical end points in 17,000 patients treated with streptokinase and randomized to adjunctive hirulog or heparin therapy.

More data are needed before direct antithrombin inhibitors can replace unfractionated heparin in patients having

acute coronary syndromes. However, there is one area in which direct thrombin inhibitors have an important place. Argatroban has become the drug of choice for patients with heparin-induced thrombocytopenia. In a large scale, non-randomized, prospective trial, argatroban reduced a combined end point of morbidity and mortality when compared with historical controls without any increase in bleeding risk [26]. This is the topic of a later paper.

References

- Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J: Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-dependent inhibitors. *J Clin Invest* 1990;86:385–391.
- Hirsh J: Heparin. *N Engl J Med* 1991;324:1565–574.
- Stone SR, Hofsteenge J: Kinetics of inhibition of thrombin by hirudin. *Biochem* 1986;25:4622–4628.
- Eriksson BI, Wille-Jørgensen P, Kalebo P, et al: A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complication after total hip replacement. *N Engl J Med* 1997;337:1329–1335.
- Serruys PW, Herrman J-PR, Simon R, et al and the Helvetica Investigators: A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty. *N Engl J Med* 1995;333:757–763.
- Lidon RM, Theroux P, Juneau M, Adelman B, Maraganore J: Initial experience with a direct antithrombin, hirulog, in unstable angina: Anticoagulant, antithrombotic, and clinical effects. *Circulation* 1993;99:1495–1501.
- Fox KA: r-Hirudin in unstable angina pectoris: Rationale and preliminary data from the APT pilot study. *Eur Heart J* 1995;16(suppl D):28–32.
- Sharma GV, Lapsley D, Vita JA, Sharma S, Coccio E, Adelman B, Loscalzo J: Usefulness and tolerability of hirulog, a direct thrombin inhibitor, in unstable angina pectoris. *Am J Cardiol* 1993;72:1357–1360.
- Fuchs J, Cannon CP, and the TIMI 7 Investigators: Hirulog in the treatment of unstable angina: Results of the Thrombin Inhibition in Myocardial Ischemia (TIMI) 7 Trial. *Circulation* 1995;92:727–733.
- Topol EJ, Fuster V, Harrington RA, et al: Recombinant hirudin for unstable angina pectoris: A multicenter, randomized angiographic trial. *Circulation* 1994;89:1557–1566.
- Lidon RM, Thérout P, Lespérance J, Adelman B, Bonan R, Duval D, Levesque J: A pilot, early angiographic patency study using a direct thrombin inhibitor as adjunctive therapy to streptokinase in acute myocardial infarction. *Circulation* 1994;89:1567–1572.
- Thérout P, Perez-Villa F, Waters D, Lespérance J, Shabani F, Bonan R: Randomized double-blind comparison of two doses of hirulog with heparin as adjunctive therapy to streptokinase to promote early patency of the infarct-related artery in acute myocardial infarction. *Circulation* 1995;91:2132–2139.
- Cannon CP, McCabe CH, Henry TD, et al: A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) 5 trial. *J Am Coll Cardiol* 1994;23:993–1003.
- Lee LV: Initial experience with hirudin and streptokinase in acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) 6 trial. *Am J Cardiol* 1995;75:7–13.
- Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators: A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;335:775–782.
- Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators: Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation: A randomized trial. *Circulation* 1997;96:769–777.
- Organisation to Access Strategies for Ischemic Syndromes (OASIS-2) Investigators: Effects of recombinant hirudin (lepirudin) compared with heparin of death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischemia without ST elevation: A randomised trial. *Lancet* 1999;353:429–438.
- Neuhaus KL, von Essen R, Tebbe U, et al: Safety observations from the pilot phase of the randomized r-Hirudin for Improvement of Thrombolysis (HIT-III) study: A study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte. *Circulation* 1994;90:1638–1642.
- GUSTO IIa Investigators: Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation* 1994;90:1631–1637.
- Antman EM, for the TIMI 9A investigators: Hirudin in acute myocardial infarction. Safety report from the thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9A trial. *Circulation* 1994;90:1624–1630.
- The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators: A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndrome. *N Engl J Med* 1996;335:775–782.
- Ferguson JJ: Meeting highlights: XIX Congress of the European Society of Cardiology. *Circulation* 1997;96:3818–3821.
- Alderman EL: Results from late-breaking clinical trials sessions at ACC '98. *J Am Coll Cardiol* 1998;32:1–7.
- Cody RJ: Results from late breaking clinical trials session at ACC '97. *J Am Coll Cardiol* 1997;30:1–7.
- White HD, Aylward PE, Collins R, et al: Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). *Circulation* 1997;96:2155–2161.
- Lewis BE, Wallis DE, Berkowitz SD, Matthai WH, Fareed J, Walenga JM, Bartholomew J, Sham R, Lemer RG, Zeigler ZR, Rustagi PK, Jang IK, Rifkin SD, Moran J, Hursting MJ, Kelton JG, for the ARG-911 Study Investigators: Argatroban Anticoagulant Therapy in Patients With Heparin-Induced Thrombocytopenia. *Circulation* 2001;103:1838–1843.